REMARKS

Reconsideration of this application is respectfully requested in view of the above amendments and following remarks.

I. Status of the Claims

Upon entry of this amendment, claims 4, 7-10, 17, 19-22 and 63-68, 72-76 and 80 are pending and at issue in this application. Claims 18, 60-62, 69-71, 77-79 and 81-84 have been canceled without prejudice or disclaimer. Claims 4, 7-9, 17, 19-21, 63-68, 72-76 and 80 have been amended for clarity. Support for these amendments can be found in the claims, as originally filed.

No new matter has been added by this amendment.

II. Claim Objections

(A) Claims 4, 7, 8 and 9 (and claims dependent thereform) are objected to, because in the Examiner's view, "A polyarginine containing crystal of human growth hormone (hGH) comprising hGH" is redundant with "comprising polyarginine and hGH." In response, Applicants have amended the claims to recite that the polyarginine is complexed with the hGH crystal, and submit that the alleged redundancy is no longer present. Accordingly, Applicants request withdrawal of this objection.

(B) Claim 7 is objected to for the use of the term "$T^{90\%}$." In response, Applicants have amended claim 7 to call for "$T_{90\%}$." Support for this amendment can be found on p. 55 of the application, as filed. Based on this amendment, Applicants request withdrawal of the objection of claim 7, and reconsideration of the claim.

(C) Claims 17-22 are objected to for the use of the phrase "and an excipient," because in the Examiner's view, "and an excipient" does not further limit the subject matter of the previous

claim. In response, Applicants have amended these claims to call for "an additional excipient" instead of "an excipient." Applicants therefore request withdrawal of this objection and reconsideration of claims 17 and 19-22.

(D) Claims 17-22 are objected to because in the Examiner's view, the claims fail to further limit the subject matter of the previous claim. Applicants have canceled claim 18 and have deleted the limitation "wherein the hGH:polyarginine ratio is 12:1 to 3:1 (w/w)" from claims 4 and 7-9. Therefore, Applicants submit that this objection is now moot.

III. Indefiniteness Rejections

In the Office Action, the Examiner rejects claims 9, 17-22, 60-63, 66, 69-72, 74, 77-80 and 82 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that "it is wholly unclear how a bioavailability *in vivo* hGH in serum would be measured by AUC when AUC is measured by UV-VIS spectrophotometer at certain wave length *in vitro*" (Office Action, p. 5). Still further the Examiner states, "the term "bioavailability" applies to both soluble and crystal form of hGH, once it is introduced to a patient, since a crystalline form of hGH would be solubilized inside the patient. Thus, if the identical dose is used, the amount of bioavailability is the same and can't be at least 50% or more" (Id.). Applicants respectfully traverse this rejection, based on the following.

Applicants respectfully disagree with the Examiner that AUC has to be measured by UV-Vis spectrophotometer. Applicants have not limited the claims to any particular method for determining AUC. Applicants assert that any method for determining the AUC for human growth hormone known to those of ordinary skill in the art at the time of filing the present application would be a suitable method for determining AUC. At the time of filing, the most common method for determining hGH serum levels was through the use of an immunoassay. An example of one such assay is shown in the submitted article, enclosed as Exhibit 1 – Vahl *et al.* (1997). "Metabolic Effects and Pharmacokinetics of a Growth Hormone Pulse in Healthy Adults: Relation to Age, Sex, and Body Composition," JCEM 82, pp. 3612-3618 (*see* page 3613, first column, first full

paragraph). Therefore, contrary to the Examiner's assertion, *in vivo* AUC can be measured specifically with an immunoassay without the fear of unwanted noise from other molecules in the sample (*see* Office Action, p. 5).

With respect to the Examiner's comments regarding "bioavailability," Applicants have amended claim 9 to indicate that the dose of the soluble form of hGH would be identical or **lower** than the comparable does of the crystallized form of hGH. Support for this amendment can be found at least in tables 6 and 17 of the application, as filed. Based on the above amendments and arguments, Applicants request withdrawal of the indefiniteness rejection and reconsideration of the rejected claims.

IV. Written Description Rejection

Claims 4, 7-10, 17-22 and 60-84 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In order to satisfy the written description requirement, an Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. MPEP §2163.02.

In the Examiner's view, the specification does not adequately describe the claimed genus of cocrystallization of hGH:polyarginine resulting in a hGH:polyarginine cocrystal, optionally having other additives (Office Action, pp. 7-8). In the interest of advancing prosecution, Applicants have amended the claims to call for an hGH crystal complexed to polyarginine. Applicants therefore note, contrary to the Examiner's assertion, that the claims as currently recited, do not encompass a cocrystal of polyarginine and hGH. Applicants further note that this amendment is made without prejudice or disclaimer, and therefore, Applicants reserve the right to pursue hGH cocrystals in other patent applications.

The Examiner also contends that Applicants have failed to describe a single example sufficiently because hGH is disclosed in the specification to have been purchased from BresaGen Ltd., and is also disclosed to encompass hGH isoforms with molecular masses of 5, 17, 20, 22, 24, 36 and 45 kDa (Office Action, p. 8). However, each of the examples is directed to the crystallization of the native hGH, having 191 amino acids, or the native 191 amino acid sequence

having an additional N-terminal methionine. Therefore, Applicants were in fact in possession of the hGH-polyarginine complexes, as called for by the present claims.

The specification describes the crystallization of hGH from at least three sources: BresaGen Ltd., and recombinant hGH isolated from either *E. coli* (Novartis) or yeast (Lucky Star) (*see* Examples). Additionally, Applicants crystallized hGH using a variety of different reagents (see Examples, 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 13, 14, 18, 20, 21, 26, and 27 (*e.g.*, ammonium phosphate, sodium citrate, sodium phosphate, protamine sulfate, zinc acetate, calcium acetate, calcium chloride, isopropanol, PEG of varying molecular weights, etc.). In addition, Applicants formed both polyarginine and protamine complexes with crystallized hGH (*see*, *e.g.*, Examples 19 and 21). Still further, Applicants tested the complexes and cocrystals using *in vivo* animal studies (see Examples 22, 23, 24 and 25). Applicants submit that these multiple examples and their corresponding figures clearly demonstrate to one skilled in the art that as of the filing date sought, Applicants were in possession of the invention, as called for by the pending claims.

Therefore, based on the specification's disclosure, as well as the data presented in the Example section of the specification, and the arguments above, it is clear that the Applicants were in possession of the claimed invention, at the time of filing the present application. For at least the reasons given above, Applicants request withdrawal of the written description rejection and reconsideration of the claims.

V. Enablement Rejection

Claims 4, 7-10, 17-22 and 60-84 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The standard for enablement is whether the application contains sufficient information to enable one of ordinary skill in the pertinent art to make and use the claimed invention without undue experimentation. Among the factors to be considered in determining whether the claims are enabled is the nature of the invention, the breadth of the claims, predictability in the art and the amount of guidance provided in the application. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Nature of the Invention and Breadth of the Claims

In the Office Action, the Examiner indicates that the disclosure is "enabling for a crystalline human growth hormone...prepared according to instant Examples 1-4, 6-8 and 10-14 and soaking or adding with a polyarginine solution, thereby forming a hGH crystal composition comprising hGH: polyarginine" (Office Action, p. 9). The Examiner also states that the disclosure is enabled for "a complex of crystalline or cocrystallized human growth hormone (hGH):polyarginine and optional agent(s) according to instant specification and prior art (Office Action, p. 11). Applicants contend that the scope of the claims, as currently recited, is commensurate in scope with the disclosure that the Examiner argues is enabled. The present claims are directed to a crystal of hGH complexed with polyarginine and the Examiner states that the disclosure is "enabling for a crystalline human growth hormone...prepared according to instant Examples 1-4, 6-8 and 10-14 and soaking or adding with a polyarginine solution, thereby forming a hGH crystal composition comprising hGH: polyarginine" (*e.g.*, a complex of an hGH crystal and polyarginine, Office Action, p. 9). Accordingly, the full claim scope is enabled according to the Examiner.

Predictability in the Art

The Examiner contends that the state of the art regarding protein crystallization was difficult and highly unpredictable. Although this may be the case as a general matter, Applicants' invention is not directed to crystallization of all proteins, it is directed, in part, to the crystallization of a few hGH species. To this end, Applicants provide numerous teachings as to how to arrive at an hGH crystal complexed with polyarginine, as called for by the present claims (*see* Examples).

Guidance in the Specification/Existence of Working Examples

As the Examiner indicates, the specification discloses methods for preparing a complex of crystalline hGH and polyarginine (Office Action, p. 16). The Examiner further states that the specification fails to provide guidance regarding alterations in the amino acid sequence, buffer, etc. Applicants note, however, that the claims as currently recited do not allow for variations in the amino acid sequence of hGH. Further, contrary to the Examiner's contention, the working examples provided in the specification are directed to crystallization of hGH in numerous buffer combinations (*see*, *e.g.*, Examples 1-15, 18). Additionally, Applicants disclose how to complex hGH crystals with polyarginine, and how to test the hGH crystals *in vivo* and *in vitro* (*see*, *e.g.*,

tables 2-7, Example 19). One of ordinary skill in the art, equipped with this guidance and knowledge, would have been able to complex the hGH crystals with polyarginine without undue experimentation.

For at least the reasons stated above, Applicants request that the enablement rejection be withdrawn and that the claims be reconsidered.

VI. Obviousness Rejection

Claims 4, 7-10, 17-22 and 60-84 are rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,849,700 ("Sørenson"), in view of U.S. Patent No. 5,788,959 ("Singh") and DeFelippis *et al.* (1998). J. Pharm. Sci. **87**, pp. 170-176 ("DeFelippis"). Applicants respectfully disagree with the Examiner, and request reconsideration, based on the following.

Applicants submit that the Examiner has not established a *prima facie* case of obviousness. Even if one of ordinary skill in the art would have been motivated to combine the three references cited by the Examiner, which Applicants do not concede, the disclosures contained therein fail to teach or suggest each and every claim limitation. The present claims are directed to polyarginine complexes of native crystallized hGH. However, none of the cited art discloses or suggests polyarginine complexes of crystallized hGH. Sørensen, while disclosing crystallized hGH, does not teach or suggest polyarginine complexes of crystallized hGH. Sørensen, in fact, is directed entirely to a pharmaceutical preparation comprising a growth hormone and histidine. Histidine is employed in cocrystal formulations to generate a stable product, which is resistant to deamidation, oxidation and cleavage of peptide bonds.

Sørensen discloses in the background that "animal growth hormone may be stabilized with various stabilizers to give decreased formation of insolubles and preservation of the soluble activity in aqueous environments," and that the stabilizer can be polyarginine (Sørensen, col. 2, ll. 63-67, *citing* U.S. Patent No. 4,816,568[1]). However, this disclosure, is not sufficient to provide one of

[1] The Sørensen specification recites "U.S. Patent No. 4,876,568." However, this appears to be a typographical error, as U.S. Patent No. 4,876,568 is directed to a focusing method for a printer, and 4,816,568, cited on the face of Sørensen, is directed to stabilization of growth hormones.

ordinary skill in the art with the requisite motivation to employ polyarginine complexed with crystallized hGH. One of ordinary skill in the art, when considering Sørensen as a whole, would have realized that the Sørensen invention was meant to cure the deficiencies of the prior art. To this end, Sørensen teaches the use of histidine to produce stable formulations, and not polyarginine (or any of the other molecules recited in the background of Sørensen). Additionally, Sørensen does not disclose or suggest polyarginine complexed with a native hGH crystal, *i.e.*, the subject matter called for by the present claims. Neither Sørensen, nor U.S. Patent No. 4,816,568 provides any indication that a crystal of hGH can be used together with polyarginine to arrive at a stable formulation. In fact, U.S. Patent No. 4,816,568 is silent regarding human growth hormone crystals.

The Examiner states in the Office Action, the art of crystallography is highly unpredictable (Office Action, p. 12). Therefore, according to the Examiner's own argument, the disclosure of polyarginine in a long list of compounds recited by Sørensen to stabilize a non-crystallized form of growth hormone hardly provides one of ordinary skill in the art the motivation to complex polyarginine with an hGH crystal, as called for by the present claims.

Singh does not cure the deficiencies of Sørensen. Singh is limited to a drug delivery device comprising a single phase matrix of two oppositely charged polymers (Singh, abstract). Additionally, Singh discloses that sustained release is achieved through electrostatic interactions or hydrophobic interactions between the two polymers (Singh, col. 3, ll. 27-40). One of ordinary skill in the art, upon considering Singh as a whole, would have recognized that both polymers were necessary for the Singh invention to work. Further, many polymers are recited by Singh, but the reference does not provide guidance as to how to choose individual polymers or polymer combinations. Additionally, the interactions between the polymers would most likely exclude the polymers from interacting with the active agent (*e.g.*, hGH), which is what is called for by the present claims (*i.e.*, a hGH polyarginine complex). The Examiner therefore appears to be picking and choosing arbitrary disclosures from Singh, instead of considering the reference in its entirety. The MPEP is clear that prior art references must be considered as a whole (MPEP §2141.02). One of ordinary skill in the art, upon considering Singh as a whole, would have at best, used both a positively charged and a negatively charged polymer in a non-crystalline hGH complex. To do otherwise would be in direct contradiction to Singh, as Singh is silent regarding a complex of

crystalline hGH with polyarginine, and Singh teaches numerous benefits of the polymer combination (Singh, col. 6, ll. 15-37).

DeFelippis does not cure the deficiencies of either Sørensen or Singh. DeFelippis is directed to a cocrystalline suspension of human insulin analogues and protamine. DeFelippis is silent regarding polyarginine complexed with insulin, let alone polyarginine complexed with an hGH crystal. As stated above, the Examiner argues in the Office Action that the art of crystallography is highly unpredictable (Office Action, p. 12). Accordingly, the disclosure of protamine in a cocrystal with insulin does not provide one of ordinary skill in the art a teaching or motivation to use protamine as an additional excipient in a formulation comprising polyarginine complexed with an hGH crystal, let alone a teaching or motivation to arrive at a formulation comprising polyarginine complexed with an hGH crystal, according to the Examiner's own arguments.

In the Applicants' view, the Examiner appears to be arbitrarily picking and choosing selected disclosures from Sørensen, Singh and DeFelippis in order to attempt to establish a *prima facie* case of obviousness. Neither Sørensen, U.S. Patent No. 4,816,568 (cited by Sørensen), Singh, nor DeFelippis provides any guidance or teaching as to why or how one would choose polyarginine from the multitude of other agents that are arguably amenable for use in an hGH crystal formulation. Nor do any of the references teach or suggest a complex of polyarginine and an hGH crystal. To arbitrarily state that these references provide one of ordinary skill in the art the teaching or motivation to prepare a polyarginine:hGH formulation, as called for by the present claims, instead of any other combination of active agent/polymer/excipient, is a form of hindsight reasoning, which has been condemned by the Supreme court. In KSR v. Teleflex, the Supreme Court held that "a factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." KSR v. Teleflex, 550 U.S. 398 (2007). The Examiner's reasoning appears to be what the KSR court explicitly warned against. Only with hindsight knowledge of the presently claimed invention, can the Examiner argue that it would have been obvious to arrive at a formulation comprising an hGH crystal complexed with polyarginine.

VII. Double Patenting

Claim 4 is rejected for nonstatutory obviousness-type double patenting as unpatentable over claims 1, 2, 4, 7 and 9-10 of copending U.S. Application No. 11/169,956 ("the '956 application"). Applicants respectfully request that this rejection be held in abeyance until a finding of allowable subject matter in the present application, or the '956 application.

CONCLUSION

Based on the above amendments and remarks, Applicants respectfully submit that no further impediments exist to the allowance of this application and, therefore, request an indication of allowability. If there are remaining issues that the Examiner believes could be addressed by conducting an interview, the Examiner is invited to contact the undersigned attorney to discuss such issues.

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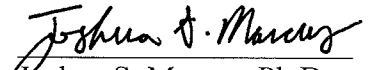
By: 
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Exhibits

- Exhibit 1 – Vahl *et al.* (1997). "Metabolic Effects and Pharmacokinetics of a Growth Hormone Pulse in Healthy Adults: Relation to Age, Sex, and Body Composition," JCEM **82**, pp. 3612-3618.